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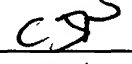

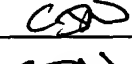

FORM PTO-1449

FIRST SUPPLEMENTAL
INFORMATION DISCLOSURE STATEMENTATTY. DOCKET NO.
1819.0030002/MAC/TSCAPPLICATION NO.
09/917,789APPLICANT
Lynch et al.FILING DATE
July 31, 2001GROUP
1493.1647




U.S. PATENT DOCUMENTS

| EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB- CLASS | FILING DATE |
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FOREIGN PATENT DOCUMENTS

| EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB- CLASS | TRANSLATION |
|---|-----|--------------------|------------|---------|-------|---------------|-------------|
|  | AL1 | WO 96/30395 A2 | 10/03/1996 | WIPO | | | Yes No |
|  | AM1 | WO 96/40737 A1 | 12/19/1996 | WIPO | | | Yes No |
|  | AN1 | WO 99/34781 A1 | 07/15/1999 | WIPO | | | Yes No |
|  | AO1 | EP 1 026 251 A2 | 08/09/2000 | Europe | | | Yes No |
|  | AP1 | WO 01/53340 A2 | 07/26/2001 | WIPO | | | Yes No |

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|---|----|---|---|
|  | AR | 1 | Bi, X., et al., "Lysosomal Protease Inhibitors Induce Meganeurites and Tangle-like Structures in Entorhinohippocampal Regions Vulnerable to Alzheimer's Disease," <i>Exp. Neurol.</i> 158:312-327, Academic Press (August 1999) |
|  | AS | 1 | Bi, X., et al., "Novel Cathepsin D Inhibitors Block the Formation of Hyperphosphorylated Tau Fragments in Hippocampus," <i>J. Neurochem.</i> 74:1469-1477, Lippincott Williams & Wilkins (April 2000) |
|  | AT | 1 | Bi, X., et al., "Rapid induction of intraneural neurofibrillary tangles in apolipoprotein E-deficient mice," <i>Proc. Natl. Acad. Sci. USA</i> 98:8832-8837, National Academy Press (July 2001) |

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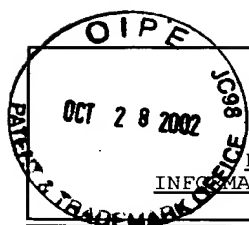
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| CDU | AL2 | WO 02/10768 A2 | 02/07/2002 | WIPO | | | Yes No |
| | AM | | | | | | Yes No |
| | AN | | | | | | Yes No |
| | AO | | | | | | Yes No |
| | AP | | | | | | Yes No |

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| CDU | AR | 2 | Coogan, A.N., et al., "The P38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of interleukin-1 β on long-term potentiation in the rat dentate gyrus <i>in vitro</i> ," <i>Neuroscience</i> 93:57-69, Elsevier Science, Ltd. (June 1999) |
| CDU | AS | 2 | Jarvik, G.P., et al., "Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: A case-control study," <i>Neurology</i> 45:1092-1096, Lippincott, Williams & Wilkins (1995) |
| CDU | AT | 2 | International Search Report for International Application No. PCT/US01/23894 mailed on June 5, 2002. |

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2/7/2003

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| | AL | | | | | | Yes No |
| CD | AM2 | WO 00/21550 A2 | 04/20/2000 | WIPO | | | Yes No |
| CD | AN2 | WO 00/21575 A2 | 04/20/2000 | WIPO | | | Yes No |
| | AO | | | | | | Yes No |
| | AP | | | | | | Yes No |

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|----|----|---|---|
| CD | AR | 3 | Ahlijanian, M.K., et al., "Hyperphosphorylated tau and neurofilament and cytoskeletal disruptions in mice overexpressing human p25, an activator of cdk5," <i>Proc. Natl. Acad. Sci. USA</i> 97:2910-2915, National Academy Press (March 2000) |
| CD | AS | 3 | Akiyama, H., et al., "Inflammation and Alzheimer's disease," <i>Neurobiol. Aging</i> 21:383-421, Elsevier Science, Inc. (May/June 2000) |
| CD | AT | 3 | Bahr, B.A., et al., "Induction of β -Amyloid-Containing Polypeptides in Hippocampus: Evidence for a Concomitant Loss of Synaptic Proteins and Interactions with an Excitotoxin," <i>Exp. Neurol.</i> 129:81-94, Academic Press, Inc. (1994) |

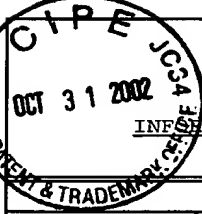
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U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

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| | AL | | | | | | Yes No |
| | AM | | | | | | Yes No |
| | AN | | | | | | Yes No |
| | AO | | | | | | Yes No |
| | AP | | | | | | Yes No |

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

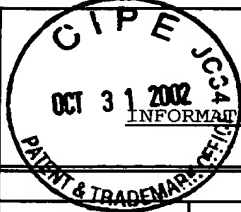



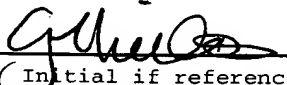
| | | | |
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| CD | AR | 4 | Bednarski, E., and Lynch, G., "Cytosolic Proteolysis of τ by Cathepsin D in Hippocampus Following Suppression of Cathepsins B and L," <i>J. Neurochem.</i> 67:1846-1855, Lippincott-Raven Publishers (1996) |
| CD | AS | 4 | Bednarski, E., et al., "Suppression of Cathepsins B and L Causes a Proliferation of Lysosomes and the Formation of Meganeurites in Hippocampus," <i>J. Neurosci.</i> 17:4006-4021, Society for Neuroscience (1997) |
| GS | AT | 4 | Bednarski, E., and Lynch, G., "Selective suppression of cathepsin L results from elevations in lysosomal pH and is followed by proteolysis of tau protein," <i>Neuroreport</i> 9:2089-2094, Rapid Science, Ltd. (1998) |

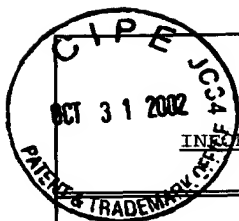
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|  | | FORM PTO-1449 | | ATTY. DOCKET NO. 1819.0030002/MAC/TSC | | APPLICATION NO. 09/917,789 | | RECEIVED NOV 01 2002 TECH CENTER 1600/291 | |
| | | INFORMATION DISCLOSURE STATEMENT | | APPLICANT Lynch et al. | | FILING DATE July 31, 2001 | | | GROUP 1425 1647 |
| | | U.S. PATENT DOCUMENTS | | | | | | | |
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| | AL | | | | | | Yes No | | |
| | AM | | | | | | Yes No | | |
| | AN | | | | | | Yes No | | |
| | AO | | | | | | Yes No | | |
| | AP | | | | | | Yes No | | |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | | | |
|  | AR | 5 | Bi, X., et al., "Lysosomal Protease Inhibitors Induce Meganeurites and Tangle-like Structures in Entorhinohippocampal Regions Vulnerable to Alzheimer's Disease," <i>Exp. Neurol.</i> 158:312-327, Academic Press (August 1999) | | | | | | |
|  | AS | 5 | Bi, X., et al., "Novel Cathepsin D Inhibitors Block the Formation of Hyperphosphorylated Tau Fragments in Hippocampus," <i>J. Neurochem.</i> 74:1469-1477, Lippincott Williams & Wilkens, Inc. (April 2000) | | | | | | |
|  | AT | 5 | Biernat, J., et al., "The switch of tau protein to an Alzheimer-like state includes the phosphorylation of two serine-proline motifs upstream of the microtubule binding region," <i>EMBO J.</i> 11:1593-1597, Oxford University Press (1992) | | | | | | |
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| | AL | | | | | | Yes No |
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| CDU | AR | 6 | Bodovitz, S., and Klein, W.L., "Cholesterol Modulates α -Secretase Cleavage of Amyloid Precursor Protein," <i>J. Biol. Chem.</i> 271:4436-4440, American Society for Biochemistry and Molecular Biology, Inc. (1996) |
| CDU | AS | 6 | Brown, M.S., and Goldstein, J.L., "Lipoprotein Metabolism in the Macrophage: Implications for Cholesterol Deposition in Atherosclerosis," <i>Ann. Review Biochem.</i> 52:223-261, Annual Reviews, Inc. (1983) |
| CDU | AT | 6 | Chin, J.Y., et al., "Microtubule-Affinity Regulating Kinase (MARK) Is Tightly Associated with Neurofibrillary Tangles in Alzheimer Brain: A Fluorescence Resonance Energy Transfer Study," <i>J. Neuropathol. Exp. Neurol.</i> 59:966-971, American Association of Neuropathologists, Inc. (November 2000) |

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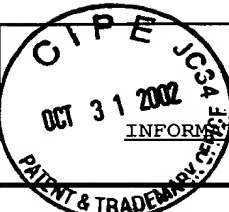
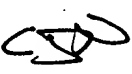


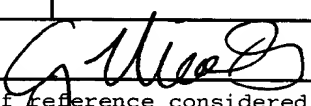
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| | AR | 7 | Eikelenboom, P., et al., "Inflammation and Alzheimer's Disease: Relationships between Pathogenic Mechanisms and Clinical Expression," <i>Exp. Neurol.</i> 154:89-98, Academic Press (1998) |
| | AS | 7 | Heffernan, J.M., et al., "Temporal Cortex Synaptophysin mRNA Is Reduced in Alzheimer's Disease and Is Negatively Correlated with the Severity of Dementia," <i>Exp. Neurol.</i> 150:235-239, Academic Press (1998) |
| | AT | 7 | Heinonen, O., et al., "Loss of synaptophysin-like immunoreactivity in the hippocampal formation is an early phenomenon in Alzheimer's disease," <i>Neurosci.</i> 64:375-384, Elsevier Science, Ltd. (1995) |

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| | | | | APPLICANT Lynch et al. | | | |
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| | AP | | | | | | Yes No |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | |
|  | AR | 8 | Hoffman, K.B., et al., " β -Amyloid increases cathepsin D levels in hippocampus," <i>Neurosci. Lett.</i> 250:75-78, Elsevier Science Ireland, Ltd. (1998) | | | | |
|  | AS | 8 | Howland, D.S., et al., "Modulation of Secreted β -Amyloid Precursor Protein and Amyloid β -Peptide in Brain by Cholesterol," <i>J. Biol. Chem.</i> 273:16576-16582, The American Society for Biochemistry and Molecular Biology, Inc. (1998) | | | | |
|  | AT | 8 | Huang, D.Y., et al., "ApoE3 binding to tau tandem repeat I is abolished by tau serine ₂₆₂ phosphorylation," <i>Neurosci. Lett.</i> 192:209-212, Elsevier Science Ireland, Ltd. (1995) | | | | |
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| CD | AR | 9 | Jicha, G.A., <i>et al.</i> , "cAMP-Dependent Protein Kinase Phosphorylations on Tau in Alzheimer's Disease," <i>J. Neurosci.</i> 19:7486-7494, Society for Neuroscience (September 1999) |
| CD | AS | 9 | Jick, H., <i>et al.</i> , "Statins and the risk of dementia," <i>The Lancet</i> 356:1627-1631, <i>The Lancet</i> (November 2000) |
| CD | AT | 9 | Manser, E., <i>et al.</i> , "A brain serine/threonine protein kinase activated by Cdc42 and Rac1," <i>Nature</i> 367:40-46, Macmillan Magazines, Ltd. (1994) |

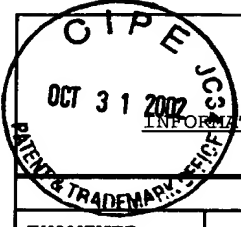




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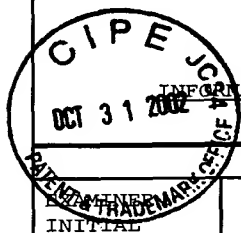
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| FORM PTO-1449 | | | | ATTY. DOCKET NO. 1819.0030002/MAC/TSC | | APPLICATION NO. 09/917,789 | |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | |
| CSU | AR | 10 | Mercken, M., et al., "Differential sensitivity to proteolysis by brain calpain of adult human tau, fetal human tau and PHF-tau," <i>FEBS Lett.</i> 368:10-14, Elsevier Science B.V. (1995) | | | | |
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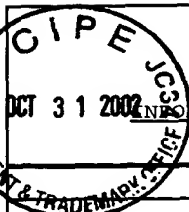
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|  | AR | 11 | Nakanishi, H., <i>et al.</i> , "Age-Related Changes in Activities and Localizations of Cathepsins D, E, B, and L in the Rat Brain Tissues," <i>Exp. Neurol.</i> 126:119-128, Academic Press, Inc. (1994) | | | | | | |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | |
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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | |
| CS | AR | 13 | Rogers, J., et al., "Inflammation and Alzheimer's Disease Pathogenesis," <i>Neurobiol. Aging</i> 17:681-686, Elsevier Science, Inc. (1996) | | | | |
| CS | AS | 13 | Sawamura, N., et al., "Site-specific Phosphorylation of Tau Accompanied by Activation of Mitogen-activated Protein Kinase (MAPK) in Brains of Niemann-Pick Type C Mice," <i>J. Biol. Chem.</i> 276:10314-10319, The American Society for Biochemistry and Molecular Biology, Inc. (March 2001) | | | | |
| CS | AT | 13 | Sternberger, L.A., and Sternberger, N.H., "Monoclonal antibodies distinguish phosphorylated and nonphosphorylated forms of neurofilaments <i>in situ</i> ," <i>Proc. Natl. Acad. Sci. USA</i> 80:6126-6130, National Academy Press (1983) | | | | |
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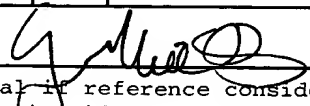
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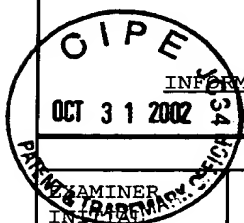
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| CSN | AR | 14 | Sternberger, N.H., et al., "Aberrant neurofilament phosphorylation in Alzheimer disease," <i>Proc. Natl. Acad. Sci. USA</i> 82:4274-4276, National Academy Press (1985) |
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| CSN | AT | 14 | Teter, B., et al., "Role of apolipoprotein E and estrogen in mossy fiber sprouting in hippocampal slice cultures," <i>Neurosci.</i> 91:1009-1016, Elsevier Science, Ltd. (July 1999) |

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| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | |
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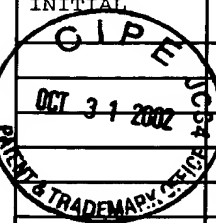

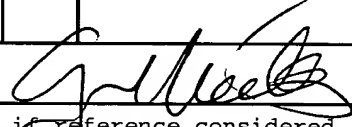
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| CD | AR | 16 | Xu, H., et al., "Generation of Alzheimer β -amyloid protein in the trans-Golgi network in the apparent absence of vesicle formation," <i>Proc. Natl. Acad. Sci. USA</i> 94:3748-3752, National Academy Press (1997) |
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| | AP | | | | | | Yes No |
| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) | | | | | | | |
|  | AR | 17 | Yong, A.P., et al., "Lysosomal Dysfunction Results in Lamina-Specific Meganeurite Formation but Not Apoptosis in Frontal Cortex," <i>Exp. Neurol.</i> 157:150-160, Academic Press (May 1999) | | | | |
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